REMARKS/ARGUMENTS

Claims 1, 4, and 16-20 are in the application. Claims 3 and 5 to 14 are held withdrawn from consideration as being drawn to non-elected subject matter. Accordingly, Claims 3 and 5 to 14 have been cancelled and applicants reserve the right to prosecute the subject matter of said claims in one or more divisional applications.

Rejection under 35 USC § 103

Claims 1 and 4 are rejected under 35 USC § 103 as being unpatentable over Kenig et al. or Boyd et al., all of record, based on court's decision *In re Adamson and Duffin,* 125 USPQ 233 (CCPA 1960). The Office Action states "that skilled artisan, knowing a compound contains an asymmetric carbon atom, possesses all resultant optical isomers". The Office Action cites *Adamson* for teaching that use of one or another optical isomer by the skilled artisan would have seen as prima facie obvious, absent some difference in kind between various isomers. Finally, the Office Action cites *In re Lohr* for requiring a showing of "clear and convincing" evidence of unexpected benefits. Scope of such evidence should reasonably commensurate with the scope of subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

Applicants respectfully assert that the cited references do not render the claimed invention obvious and traverse the rejection.

Applicant's claims are directed to a method of treating HIV-1 or HBV infection by use of the (R)-enantiomer of penciclovir triphosphate. Both the Kenig et al. and the Boyd et al. references do not disclose penciclovir triphosphate, nor do they disclose the (R)-isomer of this compound. Also these references teach different uses of penciclovir.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) when combined must teach or suggest all the claim limitations. See MPEP § 2143

The motivation or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. See MPEP § 2143.01

The CCPA addressed motivation, *In re Stemninski*, 170 USPQ 343 (CCPA 1971). The requisite motivation is not abstract, but practical, and is always related to the properties or uses

one skilled in the art would expect the compound to have, if made. Attention is directed to publication by Earnshaw et al in Antimicrobial Agents and Chemotherapy 36 (1992), 2747-2757 ("Earnshaw"). Earnshaw gives the impression that it is essentially the (S)-enantiomer of penciclovir triphosphate that is responsible for the beneficial pharmacological activity, and not the (R)-enantiomer: thus only the activities of the racemate (R,S) and of the (S)-enantiomer of the penciclovir triphosphate are investigated therein. Earnshaw is almost silent on the (R)-enantiomer, and the few conclusions arrived at , indirectly, as regards the activity of the (R)-enantiomer convey the impression that the (R)-enantiomer is not of real interest (see e.g. page 2752, col. 1, lines 1-3), being much less active against viral DNA polymerases, except perhaps somewhat as regards HSV-2 DNA polymerase (page 2752, col. 1, lines 6-7).

Moreover, on page 2752, col. 2, lines 5-15 of Earnshaw it is further shown that the (S)-enantiomer is far less inhibitory against the human cellular MRC-5 DNA polymerase α than, surprisingly, the racemate (page 2752, col. 2, lines 5-15). This observation implies that the (R)-enantiomer is more inhibitory, a clearly undesirable effect since human cellular replication would be inhibited by the (R)-enantiomer, not viral replication.

Still further, in DNA chain extension assays the (R)-enantiomer appears to be a poorer substrate than the (S)-enantiomer for both the cellular MRC-5 and the viral HSV-2 DNA polymerases (page 2752, col. 2, lines 33-37), again suggesting that that the (R)-enantiomer is not of pharmacological interest.

Thus the overall teaching of Earnshaw would lead the skilled worker away from the present invention.

Attention is further directed to the publication by Vere Hodge and Cheng in Antiviral Chem. & Chemotherapy 4 (1993) Suppl. 1, 13-24 ("Vere Hodge"), of record. While Vere Hodge emphasizes the important function of the triphosphate of penciclovir in the control of viral infection, it is either silent as regards the enantiomers of PCV-TP, or focuses on the major enantiomer, (S)-penciclovir triphosphate and its long half-life. Thus from page 18, col. 2, lines 4-16 of Vere Hodge it appears that either no labeled (R)-enantiomer formation could be detected in HSV-1 infected cells, or only up to about 10% in HSV-2 infected cells. Additionally, from page 19, col. 2, lines 23-25 it follows that the (R)-enantiomer has little HSV DNA polymerase-inhibitory activity, providing no incentive or motivation to the skilled worker for investigating further the (R)-enantiomer in herpes infections.

Again, the skilled worker having Vere Hedge before him would thus be led away from further investigating the usefulness of the (R)-enantiomer. The prior art as exemplified in Earnshaw and Vere Hedge points towards only an insignificant or subordinate biological role for

the (R)-enantiomer of penciclovir triphosphate and, therefore, provides no motivation for a skilled artisan to arrive at applicant's invention.

The Examiner does not identify support in the cited references to suggest or offer any strong motivation to resolve racemic compounds. The Office Action merely states that various optical isomers can differ in their physiological effects. There is no teaching in the cited prior art how to resolve this specific phosphate ester in enantiomerically pure form. The evaluation of efficacy of the (R)-enantiomer required development of a specific methodology. There is no suggestion or motivation in the art to arrive at the compound required in applicant's claimed method.

Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success. It is impossible to know *a priori* the efficacy of a specific optical isomer. It could not have been predicted that the (R) PCV-TP enantiomer would be a more active inhibitor of HBV DNA polymerases and HIV-1 reverse transcriptase than the (S)-enantiomer of PCV. The court in *In re Geiger*, 815 F. 2d 686,688 (Fed. Cir. 1987), held that even "though one skilled in the art might find it obvious to try various combinations" this does not meet the burden imposed on PTO. In the present case, one skilled in the art would have a reasonable basis to expect that (R)-enantiomer would be more bioactive. It was only synthesis and testing of the (S)-enantiomer that the activity could be ascertained. In fact, as discussed above, one skilled in the art would be led from investigating and obtaining in the optically pure form the (S)-enantiomer.

Moreover, there is no teaching or suggestion in the cited prior art of the specific bioprecurser phosphate esters claimed herein in Claims 4, and 16 to 20. Therefore, regardless of the allowance of Claim 1, Claims 4, and 16 to 20 are clearly patentable.

In light of these remarks, Applicants respectfully request reconsideration and withdrawal of the rejection to Claims1, 4 and 16 to 20 under 35 USC § 103 and that said claims be passed to allowance.

Respectfully submitted,

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Date: August 27, 2003